REMARKS

The Examiner objected to claims 1 to 6 as being obvious having regard to Tarelli et al. in view of Boratynski. Applicants request the withdrawal and reconsideration of this objection in view of the following remarks.

The Examiner agrees that Brodsky et al. does not use lyophilisation (vacuum) to achieve glycation. Tarelli et al. cited by the Examiner also used lyophilisation to remove water. Lyophilisation under vacuum is a standard procedure only for removing water from dissolved solutes and is particularly useful for drying solutions of proteins. There is not a single citation in the literature which claims that proteins can be glycated with the resultant formation of a ketoamine linkage by incubation at elevated temperature under vacuum, as now claimed in claim 1 as amended, of the present patent application. Support for this amendment may be found for example at page 4, lines 15-18 and page 10, lines 22-25 of the present application.

Evidence that lyophilization of proteins for the production of glycated proteins is not obvious can be inferred by reference to the following recent treatise on the subject of protein lyophilisation: Cryopreservation and Freeze Drying Protocols, Second Edition, by John G. Gay and Glyn N. Stacey, In Methods in Molecular Biology, Volume 368, Humana Press, 2007. In this exhaustive treatise there is no mention or inference of using protein lyophilisation as a procedure, or as part of a procedure, for the glycation of proteins.

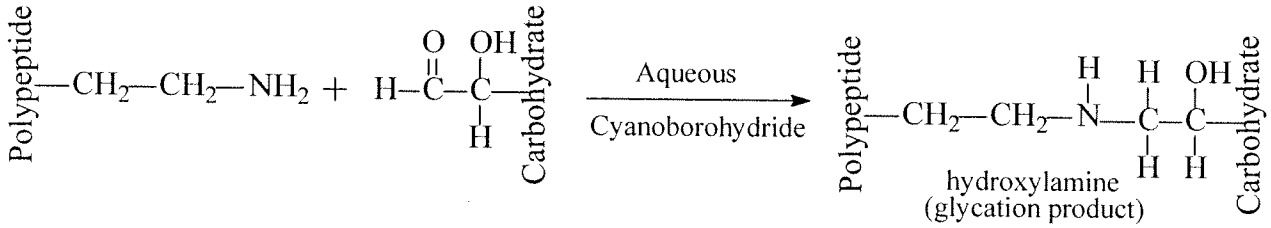
The Examiner again refers to the work of Tarelli et al. stating *" the present steps are not deemed to present any unexpected results advancing the well know peptide art of vacuum glycation of protein using a reducing sugar comprising any desired units from 1-50 therefor (Claims 1 &5) inside the pH range (claim 6) and then reducing the same with cyanoborohydride (Tarelli et al.) under known heating ranges/time frames (claims 3-4, citing Boratynski applying the heating elements for the same process, the heat range/length of time being optimizable parameters)".*

In the glycation process of Tarelli et al., referred to by the Examiner, the reaction of the reducing sugar with the amino groups on the polypeptide produced an unstable Schiff base. This Schiff base was then reduced with borohydride to form a stable hydroxylamine glycation product.

Tarelli et al.'s procedure differed from that of the inventive process in four fundamental ways as follows:

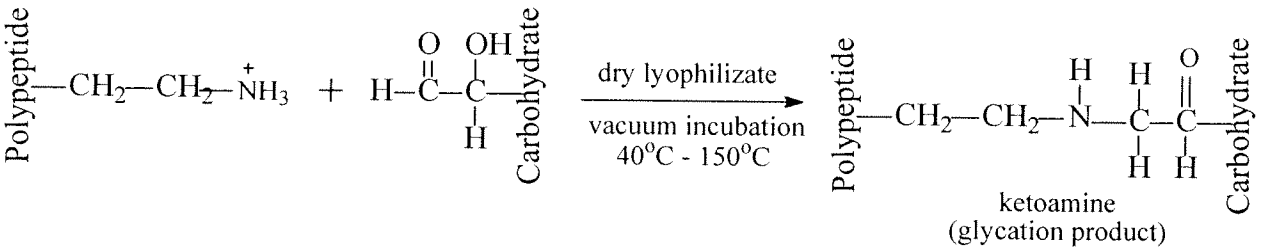
1. Tarelli et al.'s linking glycation procedure was carried out in aqueous solution not in a vacuum in the lyophilized state as in the present inventive process.
2. The glycation product is an hydroxylamine and not a ketoamine as in the patent application.
3. Reduction with cyanoborohydride was required by Tarelli et al. to produce a stable glycation product. Without this step, no stable glycated product would have been produced by Tarelli et al. In the inventive process, reduction with borohydride is not required to produce a stable glycation product.
4. The reaction mechanisms are different.

Tarelli et al. Glycation Reaction



In the inventive process in the patent application, a stable ketoamine glycation product is formed by the in vacuo incubation Claim 1, Figure 1 without the need for reduction with cyanoborohydride as required by Tarelli et. al.

In Vacuo Glycation (Inventive process)



The stable ketoamine produced by in vacuo incubation can also be reduced with borohydride to convert the keto group to a hydroxyl group but, unlike Tarelli et al., this step is not necessary to

form a stable glycated product. To avoid confusion, claim 2 has been cancelled as it is not a necessary part of the inventive process.

Applicants submit that not only are the glycation products different but also the reaction mechanisms are different. The linking reaction with Tarelli et al. occurs with a deprotonated amine whereas in the in vacuo glycation the linking reaction occurs with a protonated amine. Given the differences in products and reaction mechanism, it is respectfully submitted that the inventive process in this application is not obvious from Tarelli et al.

In the case of Boratynski et al., as noted by the Examiner, they heat a lyophilized mixture of protein and reducing sugar to achieve glycation. The procedure of Boratynski et al. differs from the inventive process in three fundamental ways.

1. Unlike in the inventive process, Boratynski et al. did not use a vacuum but heated the mixture of protein and sugar open to the atmosphere in the presence of oxygen and water.

2. Boratynski et al. obtained a large number of different products, which must differ in chemical structure and furthermore they noted that much of the product was insoluble in water. In the inventive process of the present patent application, only a single homogeneous product produced and this product is fully soluble in water.

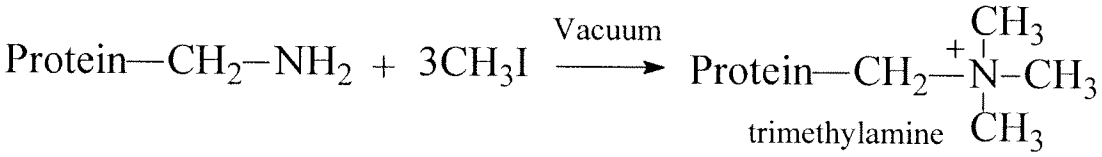
3. Boratynski et al. did not characterize the chemical linkage(s) in the products they obtained as they are a heterogeneous mixture of insoluble and soluble oxidative glycation products of undefined chemical structure. In contrast, the glycation product produced in the process of the present invention is a ketoamine (Figure 1 of patent application) as provided by the NMR evidence in figure 1 and is chemically homogeneous.

It is therefore respectfully submitted that it is not obvious from the work of Tarelli et al. and Boratynski et al. that incubation under vacuum of a lyophilized mixture of protein and reducing sugar, at the temperatures and times specified in the application, will result in a product which is

a chemically homogeneous, fully water soluble glycated protein in which sugar is covalently liked to the protein by a ketoamine bond.

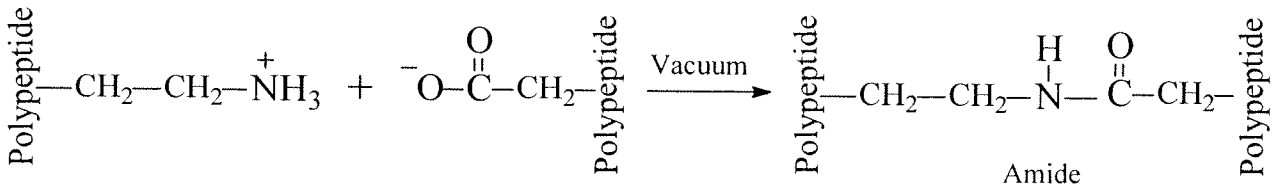
The Examiner also refers the Applicant to three of his own IDS reference submissions, namely Taralp, Alpay et al., Vakos, Helen et al., and Simons et al. as evidence for obviousness of the in vacuo glycation procedure in the patent application. Applicants request the withdrawal and reconsideration of this objection in view of the following remarks.

1. Taralp, Alpay et al.: Applicants submit that this publication deals with the reaction under vacuum of methyl iodide with a protein in which amino groups are methylated. This is not a glycation reaction and the product and chemical mechanism are not related to glycation.



2, Vakos Helen et al.,: Applicants submit that this publication is merely a variation of the procedures for the methylation of proteins under vacuum described by Taralp Alpay et al.

3. Simons et al.: Applicants submit that the reaction described in this publication is between an amino group and a carboxyl group on proteins. The linking reaction is between two protein molecules not between a protein and a sugar. The linkage formed is an amide bond not a ketoamine bond. The process here is unrelated to glycation.



While in all three of the above publications, the reaction is taking place under vacuum no reducing sugar is present and no glycation reaction is taking place. It is therefore not possible to predict from the information in these publications the product that would result, if any, when a protein and a reducing sugar are incubated in vacuo as described in the present application. For example, it is not possible to predict from 1 and 2, the product that would result from the conditions in 3. This is why reference 3 was considered to be an original contribution by Protein Science, a highly regarded Journal in the field of proteins. For the same reason, it is not possible to foresee or predict the product that would result from in vacuo incubation of protein with a reducing sugar as described in the present application because the glycation reaction is mechanistically unrelated to any of the above reactions.

Further evidence, that the use of vacuum to achieve glycation is not obvious, is provided by the following recent reviews dealing with the attachment of polysaccharides (carbohydrate) to protein. [1,2,3] These reviews summarize all the processes used in the glycation of proteins for the purposes of vaccine production, multi-billion dollar enterprises, and they do not cite a single instance of the use of in vacuo glycation nor do they mention the possibility of such a process being used. .

1. Astronomo, R.D. and D.R. Burton (2010), *Carbohydrate vaccines: developing sweet solutions to sticky situations?* Nat Rev Drug Discov, 9(4): p. 308-24.

2. Shinefield, R. (2010), *Overview of the development and current use of CRM conjugate vaccines for pediatric use.* Vaccine, 28: p, 4335-4339.

3. Fikri, Y. A. and D. L. Kasper (2010), *How Bacterial Carbohydrates Influence the Adaptive Immune System*, Ann Rev Immun., 28: p. 107-130.

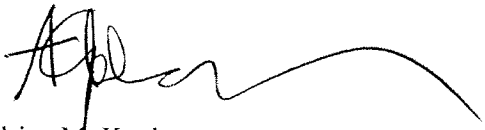
In summary, it is respectfully submitted that the inventive process is not obvious from Tarelli et al., and Boratynski et al., from any of the inventor's previous publications, or from any other source in the published literature..

CONCLUSION

In view of the Applicants' discussion , Applicants believe that the amended claims are in condition for allowance. Early notification to that effect is respectfully requested. If it is believed that a further interview will expedite prosecution, the Examiner is invited to contact Applicants' attorney Adrian M. Kaplan at Heenan Blaikie LLP, at (416) 643-6972, at her convenience.

Respectfully submitted,

Heenan Blaikie LLP



Adrian M. Kaplan
Registration No. 43,396
Agent for the Applicant

AMK

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